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Modern Concepts of Cardiovascular Disease

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EXERCISE STUDIES IN HEART DISEASE*

INTRODUCTION

During the last eight years, we have interested ourselves in the hemodynamics of exercise in health and disease; the purpose of this article is to present a resumé of some of our findings. No attempt has been made to review the important work in this field by other groups.

The subjects were studied in the supine position and performed leg work on a bicycle ergometer attached to the foot of the table. A gramophone motor and the ergometer activated the two sides of a differential indicator. This allowed a steady and predetermined rate of work to be performed, usually close to the tolerance level of the patient. Many of the patients developed high pulmonary wedge pressures but, fortunately, if the exercise is not prolonged beyond five to ten minutes, pulmonary edema does not occur. No patient was studied while in clinical congestive heart failure. The techniques of cardiac catheterization, manometry and blood and gas analysis were similar to those employed in many cardiorespiratory laboratories and are published elsewhere.[1]

The accuracy of the cardiac output measurement depends not only on the care of sampling and analysis but also on the steadiness of the subject's physiological state, particularly of the parameters employed in the Fick equation (O_2 uptake, arteriovenous oxygen content difference or A-V difference). In two series (36 subjects in each)[2] of repeated resting cardiac output determinations (range 2.4 to 12.0 l/min.) the coefficients of correlation between the first and second measurements were $r = 0.95$ and 0.94 and the standard error of a single observation was 8.1 and 7.7 per cent, respectively.

Normal Subjects

As there was a great paucity of data in normal subjects studied under exactly the same conditions, 16 subjects were investigated at rest and during various levels of exercise[3] (oxygen uptake from 220 to 1200 ml./min./sq.m.). At this time, there was uncertainty as to the period of exercise in which a steady state was achieved. The oxygen uptake was therefore determined from minute to minute and small arterial and mixed venous blood samples were drawn off at very frequent intervals. It was found that at these levels of exercise the oxygen uptake and A-V difference became relatively steady in about one minute. Thus the cardiac output could be determined with confidence in normal subjects after the second minute of exercise. The relationship of the degree of exercise, as measured by oxygen uptake, to the cardiac output is shown in Figure 1. The resting pulmonary arterial pressures were, on the whole, a little higher than previously reported (mean 18.3, S.D. 2.3 mm. Hg). It is probable that these were influenced by nervous tension as the cardiac outputs were also rather high (mean 4.4, S.D. 0.68 l/min./sq.m.). The mean pulmonary arterial pressure of the group 15-20 minutes after exercise was 16.5 mm. Hg. It is important to note, however, that under these conditions the resting mean pulmonary arterial pressure may be as high as 23 mm. Hg. The pulmonary arterial pressure rose on exercise in all but one subject. The rise was 3-8 mm. Hg up to oxygen uptakes of 564 ml./min./sq.m. At levels of oxygen uptake of 935-1160 ml./min./sq.m., two out of four subjects showed much larger increases (14 and 33 mm. Hg). Wedge pressures were not measured and thus the pulmonary vascular resistance could not be precisely determined. This work and subsequent studies of wedge pressure on exercise suggest that the pulmonary vascular resistance usually remains relatively unaltered on exercise, although it is occasionally reduced.

Another feature of interest was that the cardiac output fell near or even below "pre-exercise" levels in about one minute after exercise.

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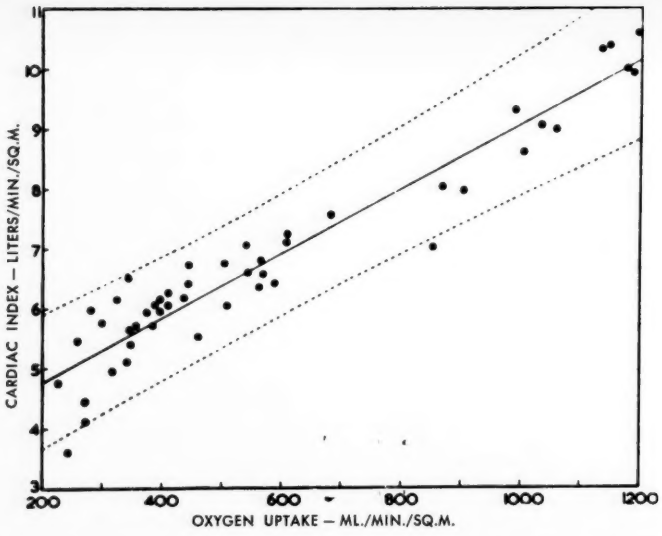

Figure 1. Cardiac output and oxygen uptake during various degrees of exercise. Values plotted for last three minutes of exercise in all 16 subjects. Gas volume N.T.P. Regression line and 95 per cent confidence limits shown.

Mitral Stenosis

The central hemodynamic findings in this disease are well known. In the early stages, there may be a normal cardiac output, both at rest and on exercise, with only a slight or moderate rise of wedge pressure (considered to be almost identical to pulmonary venous and left atrial pressure) on exercise. Some of these patients are capable of such severe and sustained effort that the high flow causes dangerous levels of pressure behind the mitral valve with risk of acute pulmonary edema. As the disease progresses, the resting wedge pressure rises and there is usually an increase in pulmonary vascular resistance, causing an even further rise of the pulmonary arterial pressure. In patients with raised pulmonary vascular resistance, who are usually also fibrillating, the cardiac output falls even in the absence of frank clinical failure. This fall of output may only be present on exercise but later is also present in the resting state.

In our studies, we investigated the problem of steadiness of state during exercise in these patients as previously described. We found that even in the most disabled patients the errors in calculating the cardiac output were unimportant in the fifth minute of exercise.[1]

A series of patients was studied in detail before and after mitral valvotomy.[4, 5] These patients had considerably raised resting and exercising pulmonary wedge and arterial pressures. The cardiac output was low normal or subnormal at rest and, in most instances, did not increase greatly on exercise. Both resting and exercising ventilation was greatly increased. Two years after successful operation and great clinical improvement, the pulmonary vascular pressures were considerably decreased but still abnormal in almost all instances. The pulmonary wedge pressures fell from the order of 40-25 to 30-15 mm. Hg. The pulmonary arterial pressures fell from figures of 70-30 to 45-20 mm. Hg. The pulmonary vascular resistance was also considerably reduced but still abnormal. The resting cardiac output was, most surprisingly, even further reduced, the mean in the group falling from 2.77 to 2.32 l/min./sq.m. The fall in cardiac output was associated with a considerable fall in resting oxygen uptake. This, in turn, was considered to be due to the reduction in respiratory work, as the resting ventilation (and perhaps compliance) was now normal.

The findings on exercise were even more disappointing. Many of these patients, who were now living normal lives, showed highly abnormal pressures on exercise. Wedge pressures of 40-50 mm. Hg and pulmonary arterial pressures of up to 80 mm. Hg were encountered in fit patients who were considered to be excellent examples of successful clinical management. Increase in the exercising cardiac output was exceptional. The exercising ventilation was, however, normal or near-normal.

Summarizing, the normal exercising ventilation was no doubt the cause of loss of dyspnea and increase of exercise tolerance. The considerable fall in pulmonary arterial pressure, combined with the further reduction of resting cardiac output, caused the resting right ventricular work to be normal in almost all instances. This low "base-line" of right ventricular work may

have allowed the still considerably increased ventricular work on exercise without the continuance or development of cardiac insufficiency. In view of the fact that many of these patients had undergone technically satisfactory valvotomies, it is possible that the circulatory adaptations to low body blood flow had remained. This, combined with the partial reduction of pressures, had critically decreased right ventricular work and also relieved the as yet unknown causes of hyperventilation.

Regional Blood Flow in Mitral Stenosis

During our studies of patients with severe mitral stenosis, we were impressed by the very low levels of mixed venous blood saturation encountered during exercise. Calculations suggested that these could only be achieved by a very considerable reduction of blood flow to parts of the body not involved in the exercise. We therefore carried out studies of the regional venous saturation at rest and during exercise in the axillary, hepatic, renal, jugular and femoral veins. Frequent small samples were taken so that the changes could be followed in great detail. It was assumed that, apart from the exercising legs, the oxygen uptakes of these regions were not altered by the brief period of exercise and that changes in regional A-V differences were inversely proportional to changes in regional blood flow. It is not possible to discuss the validity of this assumption in detail here, but it can be stated that, so far, no important evidence has emerged to discount it. Further, the changes in blood flow obtained, using this assumption in several regions of the body, are in close agreement with those obtained by other techniques. One great advantage of this method is that it allows very rapid changes of blood flow to be detected. Comparisons of the regional A-V difference in groups of abnormal subjects with those in groups of normal subjects also allow an approximate estimation of the comparative order of regional blood flow.

In the arm at rest, the A-V difference was inversely related to the cardiac output. The A-V difference was markedly increased (and blood flow decreased) in many patients with cardiac outputs in the normal range. In very disabled patients, the A-V difference was three to four times greater than the mean normal value.[6] These findings suggest that arm blood flow is reduced severely in mitral stenosis and at a very early stage. On leg exercise, normal subjects[7] and patients with normal or near-normal exercising cardiac outputs showed a transient increase of arm A-V difference, followed after two to three minutes by a considerable decrease, often below resting values. In patients with little or no increase of cardiac output on exercise, the arm A-V difference became even wider and remained so until exercise ceased.[6] There were a number of intermediate reactions with varying degrees of cardiac output response. Hand calorimetry[7, 8] confirmed that these increases of A-V difference and reduction of total arm blood flow were mainly due to changes in skin blood flow. Some of the cardiac patients, however, showed an increase in heat loss towards the end of exercise, although the total arm A-V difference remained increased. Attention was therefore turned to the arm muscle circulation. Studies of the A-V differences in the deep veins draining forearm muscle showed that although the A-V difference and presumably blood flow were normal in the disabled patients at rest, there was a marked and sustained increase of A-V difference on leg exercise. This did not occur in normal subjects.[8]

Summarizing, we concluded that during leg exercise in normal subjects there is at first a reduction of blood flow to the skin of the hand and arm followed by a pronounced increase. There is little or no change in forearm muscle blood flow. In patients with low cardiac outputs at rest and restricted cardiac output response to exercise, the blood flow to the skin is markedly reduced at rest while the forearm blood flow is relatively normal. Leg exercise results in the reduction of both skin and muscle blood flow. As exercise continues, the muscle blood flow remains low but the skin blood flow increases, although this increase is later and smaller than in normal subjects, particularly those with the most restricted cardiac outputs.

The splanchnic A-V difference was next studied. In the normal subjects,[9] the splanchnic A-V difference did not increase during leg exercise until levels involving an oxygen uptake of over 1000 ml./min./sq.m. were reached. However, even at lower levels of exertion there was a definite and sustained increase of A-V difference *after* exercise. In the patients with mitral stenosis[10] and restricted cardiac outputs, there was a very great increase of splanchnic A-V difference at relatively low levels of exercise. Hepatic venous blood saturations of less than 10 per cent were encountered. These patients showed a prolonged widening of splanchnic A-V difference after exercise. It was concluded that in normal subjects, a reduction of splanchnic blood flow does not occur until fairly high levels of exertion are reached. The decrease of blood flow afterwards was considered to be probably due to the diversion of blood to the skin (heat loss) and to recently exercised muscles. It will be remembered that the cardiac output falls rapidly to resting levels after exercise. The patients with low fixed cardiac outputs show a very great decrease of splanchnic blood flow on exercise. Judging by the A-V differences, the blood flow fell from resting levels of 50 to 25 per cent of the normal resting splanchnic flow.

Owing to the high renal blood flow, the changes in renal venous saturation on exercise were not so marked. In the disabled patients, however, there was a definite and immediate increase of A-V difference at the commencement of exercise, returning to the resting value almost immediately afterwards.[11] The studies showed that the renal blood flow fell more markedly than in normal subjects, exercising levels of 25 per cent of normal resting flow being found during quite moderate exercise.

At rest, the jugular A-V difference[11] (catheter tip in the jugular bulb) was only slightly increased in a group of moderately and severely disabled patients with mitral stenosis. The mean value suggested that the resting cerebral blood flow was about 80 per cent of normal. On exercise, there was no definite change of jugular A-V difference, even in the most disabled patients. This would suggest that, as in normal subjects, the cerebral blood flow is unaltered on exercise, even in the presence of a low fixed cardiac output.

Finally, the femoral A-V difference[12] was studied. In both normal subjects and cardiac patients, the femoral venous saturation fell to relatively low levels within one minute of the commencement of leg exercise. In the normal subjects, there was a rise of femoral venous saturation (decrease of A-V difference and increase of blood flow) as exercise proceeded and this was considered to be due to an increase in skin circulation, as occurs in the arm. In the patients with low exercising cardiac outputs, the femoral venous saturation was lower (A-V difference greater) at a given level of exercise and remained at this level throughout exercise. The steady femoral venous saturation and A-V difference was considered to be due to the persistence of skin vasoconstriction. In some of the patients with low fixed cardiac outputs, femoral venous blood, which contained no oxygen whatsoever, was obtained during several minutes of work. They continued the leg exercise without discomfort. Approximate estimations of leg blood flow were obtained by application of the Fick principle, thus:

$$\textit{Exercising leg blood flow} = \frac{O_2 \textit{ uptake of leg}}{\textit{Ex. A-V diff.}} = \frac{\textit{R.B.F.} \times \textit{R.A-V diff.} + \textit{excess } O_2 \textit{ uptake}}{\textit{Ex. A-V diff.}}$$

Resting blood flow (R.B.F.) was estimated from previous plethysmographic estimates and is not critical. It was assumed that all excess oxygen uptake was in the legs and that the femoral A-V difference was representative of all leg muscles involved. In the supine position, the glutei are not used during leg work and, in any case, if the A-V difference of muscles used outside the leg is of the order of the femoral A-V difference, then this calculation will give the blood flow of all exercising muscles. In view of the different behavior of skin blood flow, the leg blood flow was calculated in both the second and fifth minute. In five normal subjects at a given level of exercise (630 ml./min./sq.m.), the mean leg blood flow was 5.0 l/min. in the second minute and increased to 6.6 l/min. in the fifth minute. In five patients with low and almost fixed cardiac outputs during leg exercise of the same order, the mean leg blood flow was 4.1 l/min. in the second minute and 3.9 l/min. in the fifth minute. In view of the fact that skin vasoconstriction is most marked in the normal subject early in exercise, the figures in the second minute almost certainly represent more closely the comparative muscle blood flow.

It is thus apparent that even in patients with low and unchanging cardiac outputs, the exercising muscle blood flow is remarkably maintained (80 per cent of normal). This is achieved by a very considerable reduction of blood flow to the whole skin, to resting muscle, to the splanchnic area and to the kidneys. The cerebral blood flow is, however, maintained at the resting level. The repeated marked reduction of blood flow to the liver and kidneys in the more disabled patients may well have an adverse effect on hepatic and renal function. The tissue oxygen tension will be reduced whenever the patients exert themselves, particularly in the liver where the venous saturations are much lower and the effect is sustained after exercise.

Coarctation of the Aorta

A careful study has been carried out on a large series of young fit patients with uncomplicated coarctation of the aorta.[13] It was found that many patients with normal or near-normal resting brachial arterial pressures had a very marked rise of mean pressure on exertion. In those patients with mean exercising brachial arterial pressures over about 160 mm. Hg, there was evidence of incipient left ventricular insufficiency insofar as the wedge pressure became significantly raised. This is considered to be due to a rise in the left ventricular diastolic and filling pressure. Further, the peak systolic pressures on exercise were extremely high, exceeding 300 mm. Hg in a number of instances. These peak systolic pressures almost certainly can cause repeated damage to the aortic wall, which may lead to subsequent degenerative changes, dilatation and aortic valve regurgitation. After operation, there was the usual complete or partial return to normal resting arterial pressures. The exercising arterial pressures were also far lower and the wedge pressure on exercise was also normal. The peak systolic pressures, although still abnormal, were also markedly reduced.

These findings would appear to support strongly early operation before aortic damage

and left ventricular insufficiency become severe. They further emphasize the dangers of clinical decisions founded solely on observations at rest.

Essential Hypertension

A series of patients with severe essential hypertension were studied.[14] They were arbitrarily divided into two main groups: The first contained the patients without any marked degree of left ventricular enlargement or marked dyspnea on exercise. These less disabled patients had normal cardiac outputs and pulmonary arterial and wedge pressures at rest. They showed a normal response of cardiac output to exercise, although the wedge pressure became elevated in most instances. The second group consisted of patients who were severely disabled by exertional dyspnea and the majority of whom had considerable cardiac enlargement. They had lower and in some cases subnormal (below 2.5 l/min./sq.m.) cardiac outputs at rest. The resting wedge pressure was raised in some instances and normal in others. All these disabled patients showed an impairment of cardiac output response and a rise in pulmonary wedge pressure on exercise. It would thus appear that a large heart and marked shortness of breath is, not surprisingly, good evidence of considerable left ventricular insufficiency. It is important, however, to note that patients without marked cardiac enlargement or shortness of breath may have objective evidence of left ventricular insufficiency on exercise.

Exercise studies before and after the administration of antihypertensive drugs are not completed but the findings are of considerable interest.[15] Patients who are "controlled" by ganglion-blocking agents (hexamethonium, Ansolysen) and are living fairly normal lives outside the hospital show varying degrees of return to normal arterial pressures in the standing position. However, almost without exception, if they lie down their arterial blood pressures and hemodynamic behavior are similar to those already described before treatment, both at rest and on exercise. If patients are given ganglion-blocking agents in the supine position until the blood pressure is at normal levels, then the cardiac output is found to be greatly decreased and the peripheral vascular resistance relatively unchanged. The main effect appears, therefore, to be due to a redistribution of blood with its effect on the cardiac output. If the patient who has been rendered normotensive in the supine position is exercised, then, at higher levels of exertion, he shows considerable distress with no increase of cardiac output and obvious peripheral vasoconstriction (pallor and sweating). The wedge pressure does not rise on exercise, suggesting a state not very dissimilar to oligemic "shock." Exercise studies on the chronically "controlled" patients in the vertical position are to be carried out. However, these studies indicate already that these ganglion-blocking agents do not have a simple direct effect on systemic arteriolar resistance and that the fall in arterial pressure is mainly related to the abnormal pooling of blood and decreased cardiac output.

A minority of fortunate patients have been controlled by Rauwolfia derivatives alone. In this case, the fall in blood pressure is not posture dependent. In the supine position, the resting cardiac output is normal and the systemic vascular resistance normal or near-normal. On exercise, the cardiac output and blood pressure rise within normal limits and the systemic vascular resistance falls slightly as in normal subjects. It is clear that these patients, in striking contrast to those on ganglion-blocking agents, have almost normal hemodynamic and arteriolar behavior.

Hyperkinetic States

The clinical and hemodynamic findings in the hyperkinetic state have been known for many years. Little work, however, has been carried out on the effects of exercise in such patients. They may continue to lead a relatively normal life over considerable periods and it is during exercise that they often first notice untoward symptoms. Patients with severe anemia, thyrotoxicosis and arteriovenous communication were therefore studied.[16]

All anemic patients with resting cardiac outputs above 4.6 l/min./sq.m. showed abnormally high cardiac output responses to exercise (196-140 per cent of predicted). This regular relationship of abnormal resting and exercising cardiac outputs would indicate that the hyperkinetic response, once established, is present in all grades of activity. It was found that there was an increase of stroke volume both at rest and on exercise and this, rather than an increased heart rate, appeared to be the keystone of the hyperkinetic state. The increased output was maintained without abnormal filling pressures (wedge and atrial), either in the left or right heart. The vascular pressures were lowered, particularly in the systemic circulation, and this was considered to be due to the decrease of blood viscosity and perhaps systemic vasodilatation. As a result of this, the right and left ventricular pressures were normal at rest. However, on exercise, both the right and left ventricular work was almost always increased. The clinical observation that these patients can tolerate remarkable degrees of anemia and hyperkinemia while at rest, and the dramatic recovery from failure when such patients are put to bed, would appear to be related to these findings.

Patients with thyrotoxicosis and raised cardiac outputs at rest also showed abnormally high car-

diac outputs on exercise. The resting pulmonary arterial pressures were rather high and this may have been due to normal blood viscosity and lack of pulmonary vasodilatation. Thus, the right ventricular work was abnormally high in all patients studied, both at rest and on exercise. Owing to the low systemic resistance, the left ventricular work was normal in the resting state and usually, but not always, on exercise. These findings would explain the clinical experience that the right ventricle is the more embarrassed in this disease.

The patients with abnormal arteriovenous communication also showed raised cardiac outputs, both at rest and on exercise. The right ventricular work was again slightly raised (normal blood viscosity), but owing to the low systemic pressures the left ventricular work was normal both at rest and on exercise. These findings would again explain why some patients with considerable arteriovenous communication continue to enjoy good health until old age. It would appear inadvisable to assume that there is dangerous overloading of the heart in all such patients and careful investigation should precede any corrective operation that may be unduly hazardous.

DISCUSSION

It is hoped that this account of some of our work on cardiovascular problems will help to emphasize the importance of exercise studies. Providing that reasonable care and precautions are taken, studies under the stress of exercise are far more informative than those at rest alone. Some of this work involves the study of a particular disease rather than individual clinical problems. However, if reliable data are obtained, this is of great value subsequently in making important clinical decisions. There is still not enough systematic attack on the hemodynamic problems in common diseases such as mitral stenosis (both before and after operation), and essential hypertension. As has been shown again and again, the information derived from the detailed study of a relatively small series of patients is of far greater value than the "clinical impressions" derived from very large groups of patients. Cournand, Richards and Forsmann have given us a very valuable investigative tool and it should be used more fully in the unremitting fight against disease.

SUMMARY

A series of studies of the hemodynamics of normal subjects and patients with various cardiovascular diseases during exercise is described. Particular attention is given to the adaptations of regional circulation during exercise in patients with low cardiac outputs.

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REFERENCES

1. Donald, K. W., Bishop, J. M., and Wade, O. L.: Study of minute to minute changes of arteriovenous oxygen content difference, oxygen uptake and cardiac output and rate of achievement of steady state during exercise in rheumatic heart disease. J. Clin. Invest. **33**: 1146, 1954.
2. Donald, K. W., Bishop, J. M., Cumming, G., and Wade, O. L.: Effect of nursing positions on cardiac output in man, with note on repeatability of measurements of cardiac output by direct Fick method and with data on subjects with normal cardiovascular system. Clin. Sc. **12**: 199, 1953.
3. Donald, K. W., Bishop, J. M., Cumming, G., and Wade, O. L.: Effect of exercise on cardiac output and circulatory dynamics of normal subjects. Clin. Sc. **14**: 37, 1955.
4. Donald, K. W., Bishop, J. M., Wade, O. L., and Wormald, P. N.: Cardiorespiratory function two years after mitral valvotomy. Clin. Sc. **16**: 325, 1957.
5. Wade, O. L., Bishop, J. M., and Donald, K. W.: Effect of mitral valvotomy on cardiorespiratory function. Clin. Sc. **13**: 511, 1954.
6. Donald, K. W., Bishop, J. M., and Wade, O. L.: Changes in oxygen content of axillary venous blood during leg exercise in patients with rheumatic heart disease. Clin. Sc. **14**: 531, 1955.
7. Bishop, J. M., Donald, K. W., Taylor, S. H., and Wormald, P. N.: Blood flow in the human arm during supine leg exercise. J. Physiol. **137**: 294, 1957.
8. Muth, H. A., Wormald, P. N., Bishop, J. M., and Donald, K. W.: Further studies of blood flow in the resting arm during supine leg exercise. Clin. Sc. **17**: 603, 1958.
9. Bishop, J. M., Donald, K. W., Taylor, S. H., and Wormald, P. N.: Changes in arterial-hepatic venous oxygen content difference during and after supine leg exercise. J. Physiol. **137**: 309, 1957.
10. Bishop, J. M., Donald, K. W., and Wade, O. L.: Changes in oxygen content of hepatic venous blood during exercise in patients with rheumatic heart disease. J. Clin. Invest. **34**: 1114, 1955.
11. Bishop, J. M., Wade, O. L., and Donald, K. W.: Changes in jugular and renal arteriovenous oxygen content difference during exercise in heart disease. Clin. Sc. **17**: 611, 1958.
12. Donald, K. W., Wormald, P. N., Taylor, S. H., and Bishop, J. M.: Changes in oxygen content of femoral venous blood and leg blood flow during leg exercise in relation to cardiac output response. Clin. Sc. **16**: 567, 1957.
13. Taylor, S. H., and Donald, K. W.: Hemodynamics at rest and on exercise in coarctation of the aorta before and after operation. Brit. Heart J.: in press.
14. Taylor, S. H., Donald, K. W., and Bishop, J. M.: Circulatory studies in hypertensive patients at rest and during exercise, with a note on the Starling relationship in the left ventricle in essential hypertension. Clin. Sc. **16**: 351, 1957.
15. Taylor, S. H., Reeves, T. J., and Donald, K. W.: Effect of antihypertensive drugs on arterial blood pressure and hemodynamics during rest and exercise. In preparation.
16. Bishop, J. M., Donald, K. W., and Wade, O. L.: Circulatory dynamics at rest and on exercise in hyperkinetic states. Clin. Sc. **14**: 329, 1955.

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